Direct conversion of mouse fibroblasts to self-renewing, tripotent neural precursor cells.

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Public Summary:
The efficient generation of clinically relevant cell types from easily accessible patient specific tissue is a major goal of regenerative medicine. Neural stem cells are an excellent candidate for such an approach as they have many modeling and clinical applications for the treatment of neurological disorders, but are an extremely rare population in the adult brain which are technically difficult to isolate. Over the past year we have sought to directly convert fibroblasts, - an easily obtainable skin derived cell type - into neural stem cells by the forced expression of a set of lineage specific transcription factors. We have been successful in deriving a population of cells that have many of the properties of neural stem cells including the ability to differentiate into the three neural tissues found in the brain -- oligodendrocytes, astrocytes, and neurons –, the ability to be grown to large quantities, and, importantly, their ability to engraft and integrate into the mouse brain. As we have shown that direct conversion of skin cell derived fibroblasts to neural stem cells is possible in mice, we are now attempting to do the same in humans where this can be used to understand and treat patient specific neurological diseases.

Scientific Abstract:
We recently showed that defined sets of transcription factors are sufficient to convert mouse and human fibroblasts directly into cells resembling functional neurons, referred to as "induced neuronal" (iN) cells. For some applications however, it would be desirable to convert fibroblasts into proliferative neural precursor cells (NPCs) instead of neurons. We hypothesized that NPC-like cells may be induced using the same principal approach used for generating iN cells. Toward this goal, we infected mouse embryonic fibroblasts derived from Sox2-EGFP mice with a set of 11 transcription factors highly expressed in NPCs. Twenty-four days after transgene induction, Sox2-EGFP(+) colonies emerged that expressed NPC-specific genes and differentiated into neuronal and astrocytic cells. Using stepwise elimination, we found that Sox2 and FoxG1 are capable of generating clonal self-renewing, bipotent induced NPCs that gave rise to astrocytes and functional neurons. When we added the Pou and Homeobox domain-containing transcription factor Brn2 to Sox2 and FoxG1, we were able to induce tripotent NPCs that could be differentiated not only into neurons and astrocytes but also into oligodendrocytes. The transcription factors FoxG1 and Brn2 alone also were capable of inducing NPC-like cells; however, these cells generated less mature neurons, although they did produce astrocytes and even oligodendrocytes capable of integration into dysmyelinated Shiverer brain. Our data demonstrate that direct lineage reprogramming using target cell-type-specific transcription factors can be used to induce NPC-like cells that potentially could be used for autologous cell transplantation-based therapies in the brain or spinal cord.

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